

### **AMENDMENTS TO THE DRAWINGS**

The attached drawing sheet include changes to Fig. 5. The replacement sheet contains Fig. 5A-5C, and replaces the original drawing sheet. In Figure 5, previously omitted labels 5A, 5B, and 5C have been added.

## **REMARKS/ARGUMENTS**

This Amendment and Response is responsive to the non-final Office action mailed November 10, 2009, setting forth a shortened three-month statutory period for reply. A petition and fee for a three-month extension of time to reply accompany this Amendment and Response.

Claims 1-72 are pending in the application, with claims 1, 31, 54, 61, 66, 70, 72 being independent claims. Claims 1-30, 47, and 49-72 were previously withdrawn from consideration. By this Amendment no claims are cancelled, and claims 31, 32-36, 43, and 45 are currently amended. Claims 73-74 are newly added.

No new matter has been added. Support for amendment to claim 31, and newly added claims 73 and 74 may be found throughout the Specification and claims as filed, for example, Example 10, paragraphs [0239]-[0263], and claim 13.

### **I. Claim Objection**

The Examiner has requested correction of claim 43 for the reason that it does not end in a period. Claim 43 is currently amended to end in a period.

### **II. Rejection under 35 U.S.C. § 112**

Claims 33-36, 43 and 45 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 is rejected because the Examiner states, "the limitation 'the marker is alkaline phosphatase', does not have proper antecedent basis in the claim from which claim 33 depends. Claim 33 has been amended to depend from claim 32. Claim 32 recites "of a marker indicative of osteoblastic or chondrocytic differentiation." Thus, there is sufficient antecedent basis to claim "the marker is alkaline phosphatase" in claim 33, and claim 32 now recites that which was implicit.

The Examiner states, "[e]ach of claims 34-36 are directed to the modified bone matrix of claim 31 and further state the expression of 'the marker' is varied." The Examiner argues that it is unclear whether "claims 34-36 are intended to depend from claim 32 or 33, or from another claim." Claims 34-36 have been amended to depend from claim 32, which recites "a marker

indicative of osteoblastic or chondrocytic differentiation.” Thus, the antecedent basis of “the marker” is clear.

The Examiner rejects claims 34-36 because, “it is unclear what the expression level of ‘the marker’ is being compared to.” Claims 34-36 have been amended to make explicit that which was previously implicit, that is, marker expression in undifferentiated cells treated with modified bone matrix is being compared to marker expression in undifferentiated cells treated with BMP-2, 10% fetal bovine serum, or inactivated bone matrix, as recited in claims 34, 35, and 36, respectively.

The Examiner rejects claim 43 because “there is insufficient antecedent basis for” “the limitation ‘the unmodified bone matrix.’” Claim 43 depends from 31 but does not recite an “unmodified bone matrix.” Claim 31 has been amended to recite “an unmodified control bone matrix.”

Claim 45 is rejected because “it cannot be determined from claim 45 whether the ‘species’ is that of animal, chemical, etc.” Claim 45 is currently amended to recite “in an animal species.”

### III. Claim Rejections Under 35 U.S.C. § 102

Claims 31-36, 38-46, and 48 have been rejected under 35 U.S.C. § 102(b) as being anticipated by O’Leary et al. (US 5,236,456, hereinafter “O’Leary”) and/or Landesman et. al. (hereinafter “Landesman”).

According to the M.P.E.P. “[a] claim is anticipated only if each and every” aspect of the claim “is found, either expressly or inherently described,” within a single cited reference. § 2131 (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed.Cir. 1987)).

#### A. **O’Leary does not recite a “bone matrix that has been exposed to a cleavage agent to produce a modified bone matrix . . . [with increased] biological activity.”**

Claims 31, 38-42, and 48 have been rejected under 35 U.S.C. § 102(b) as being anticipated by O’Leary. The Examiner cites O’Leary for “disclos[ing] an osteogenic composition comprising demineralized bone matrix which has been subjected to an acid treatment and then heated . . . resulting . . . [in] a liquid surface-adherent osteogenic composition.” The Examiner argues that “[s]urface-adherent capability, per se, is considered a ‘biological activity,’” and that due to the increased surface adherence, the composition of O’Leary “increase[d] the osteoinductivity of the osteogenic composition.”

As currently amended, claim 31 recites “bone matrix that has been exposed to a cleavage agent to . . . [increase] biological activity.” O’Leary is not cited for teaching a cleavage agent, nor does O’Leary teach such modification. The Examiner’s rejection should be withdrawn.

**B. Landesman does not expressly or inherently teach each and every aspect of the presently claimed “bone matrix that has been exposed to a cleavage agent to produce a modified bone matrix . . . [with increased] biological activity . . . , and wherein the cleavage agent is chosen from the group consisting of collagenase and CNBr.”**

Claims 31-36, 38-40, 43-46, and 48 were rejected by the Examiner under 35 U.S.C. § 102(b) as being anticipated by Landesman. The Examiner cites Landesman for teaching a method that “is identical to the method reported in the instant disclosure to yield the currently claimed modified demineralized bone matrix having a level of at least one biological activity being increased relative to its level in a control (i.e. non-collagenase treated).” Applicants disagree.

Landesman does not teach the modified bone matrix as currently amended. On the contrary, Landesman states in its Summary that treatment with “collagenase . . . abolished [osteoinductive] activity.” p. 348. Thus, Landesman does not teach each and every aspect of the currently claimed modified bone matrix composition.

The Examiner argues that “the collagenase-treated demineralized bone matrix of Landesman et al is considered to be inherently identical to the modified bone matrix of claim[] 31.” Further, the Examiner states that “products of identical chemical composition can not have mutually exclusive properties.” This is incorrect.

Contrary to the current claims, Landesman teaches that collagenase treatment “abolished” biological activity, while the Applicant teaches and demonstrates in Example 10, that collagenase treatment enhances biological activity. These properties are indeed mutually exclusive. Further, the collagenase digestion methods of Landesman and Applicant are not identical.

Further, Landesman does not teach the use of CNBr as a cleavage agent increasing the biological activity of bone matrix.

Thus, because Landesman does not teach each and every aspect of the currently claimed modified bone matrix, and the methods of Landesman are not identical and provide for contrary properties, Landesman does not anticipate the current claims.

#### IV. Rejection under 35 U.S.C. § 103

Claims 31 and 37 were rejected under 35 U.S.C. § 103(a) as being unpatentable over O'Leary and Landesman.

**A. O'Leary and Landesman collectively do not teach “[a] modified bone matrix that has been exposed to a cleavage agent to produce a modified bone matrix, wherein the level of at least one biological activity . . . is increased . . . , wherein the cleavage agent is chosen from the group consisting of collagenase and CNBr.”**

A proper obviousness rejection based on a rationale of combining prior art elements requires at least “a finding that the prior art included each element claimed . . . with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements.” MPEP § 2143(A); *see also In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974); *CFMT, Inc. v. YieldUp Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003).

The cited references do not teach “a bone matrix that has been exposed to a cleavage agent . . . wherein the level of at least one biological activity . . . is increased . . . , wherein the cleavage agent is chosen from the group consisting of collagenase and CNBr.” As described above, O'Leary does not teach digestion of the DBM with any cleavage agent. Landesman does not teach CNBr cleavage, and further teaches that collagenase digestion of DBM “abolished” rather than increased biological activity. For at least these reasons, the Examiner's rejection is inapposite and should be withdrawn.

**B. The references teach away from treating bone matrix with collagenase to increase at least one biological activity.**

According to the M.P.E.P., cited references must be considered in their “entirety, i.e., as a whole, including portions that would lead away from the claimed invention.” § 2141.02 (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)). “A finding that a reference teaches away can preclude a finding that the reference renders a claim obvious.” *In re Chapman*, 595 F.3d 1330, 1337 (Fed.Cir. 2010); *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed.Cir. 2009) (“An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements.”).

Landesman is explicit in its teaching that collagenase reduces biological activity of DBM. Specifically, Landesman states in the Summary that treatment of DBM with “collagenase . . . abolished [osteoinductive] activity.” p. 348. In fact, in Table 2, Landesman presents experimental data showing the magnitude of collagenase treatment's detrimental effect on

osteoinductive potential. p. 352 (showing that undigested DBM resulted in 1.46 U/mg alkaline phosphatase staining, while collagenase treatment reduced staining to only 0.09 U/mg). These results, showing a greater than 90% decrease in alkaline phosphatase staining, demonstrate that osteoinductivity of DBM is significantly reduced upon collagenase digestion. These teachings would lead one of skill in the art away from the use of collagenase to create a modified bone matrix with increased biological activity.

Landesman's teaching that collagenase treatment of DBM "abolished," rather than increased, biological activity of bone matrix, precludes a finding of that the current claims are obvious. The Examiner's rejection should be withdrawn.

**C. One of skill in the art, familiar with Landesman, would not reasonably expect to digest bone matrix with collagenase and increase at least one biological activity.**

The M.P.E.P. states that references "can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success." § 2143.02 (citing *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). To support a prima facie case of obviousness, it is not enough to simply identify all aspects of the claim in the cited references. M.P.E.P. § 2143. "An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed.Cir. 2009).

One of skill in the art, in light of Landesman's teachings, would not reasonably expect that collagenase treatment of DBM would result in a modified bone matrix with increased biological activity. On the contrary one of skill in the art, familiar with Landesman, would understand that treatment of DBM with collagenase "abolished" biological activity.

Because Landesman can not create a reasonable expectation of increasing biological activity of bone matrix by digesting the DBM with collagenase as taught by Landesman, the current claims are not prima facie obvious. The Examiner's rejection should be withdrawn.

## **V. Double Patenting Rejection**

Claims 31, 38-40, 42, 43 and 48 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 73, 77, 83 and 84 of copending Application No. 12/140,025.

Because the present case is pending, and subject to continued prosecution which may obviate any substantive ground for obvious-type double-patenting, Applicants respectfully request that the provisional rejection be held in abeyance until allowable subject matter has been found in the instant applications.

**CONCLUSION**

This application now stands in allowable form and reconsideration and allowance is respectfully requested.

This response is being submitted on or before May 10, 2010, with the required fee of \$ for a three-month extension of time, making this a timely response. It is believe that no additional fees are due in connection with this filing. However, the Commissioner is authorized to charge any additional fees, including extension fees or other relief which may be required, or credit any overpayment and notify us of same, to Deposit Account No. 04-1420.

Respectfully submitted,

**DORSEY & WHITNEY LLP**  
**Customer Number 25763**

Date: 5/6/10

By: Kenneth E. Levitt  
Kenneth E. Levitt, Reg. No. 39,747  
(612) 340-2755